Oxalate Nephropathy Associated with Chronic Pancreatitis

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Summary

Background and objectives Enteric overabsorption of oxalate may lead to hyperoxaluria and subsequent acute oxalate nephritis (AON). AON related to chronic pancreatitis is a rare and poorly described condition precluding early recognition and treatment.

Design, setting, participants, & measurements We collected the clinical characteristics, treatment, and renal outcome of 12 patients with chronic pancreatitis–associated AON followed in four French renal units.

Results Before AON, mild to moderate chronic kidney disease was present in all patients, diabetes mellitus in eight (insulin [$n = 6$]; oral antidiabetic drugs [$n = 2$]), and known chronic pancreatitis in only eight. At presentation, pancreas imaging showed gland atrophy/heterogeneity, Wirsung duct dilation, calcification, or pseudocyst. Renal findings consisted of rapidly progressive renal failure with tubulointerstitial profile. Acute modification of glomerular filtration preceded the AON (*i.e.*, diarrhea and diuretics). Increase in urinary oxalate excretion was found in all tested patients and hypocalcemia in nine (<1.5 mmol/L in four patients). Renal biopsy showed diffuse crystal deposits, highly suggestive of oxalate crystals, with tubular necrosis and interstitial inflammatory cell infiltrates. Treatment consisted of pancreatic enzyme supplementation, oral calcium intake, and an oxalate-free diet in all patients and renal replacement therapy in five patients. After a median follow-up of 7 months, three of 12 patients reached end-stage renal disease.

Conclusion AON is an under-recognized severe crystal-induced renal disease with features of tubulointerstitial nephritis that may occur in patients with a long history of chronic pancreatitis or reveal the pancreatic disease. Extrinsic triggering factors should be prevented.

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Introduction

Hyperoxaluria is a serious metabolic condition. Primary hyperoxaluria results from inherited endogenous oxalic acid overproduction. Secondary hyperoxaluria mainly occurs in digestive diseases leading to increased intestinal absorption (enteric hyperoxaluria) (1,2). All these conditions lead to accumulation of oxalate within the body. The kidney is the main target organ because oxalate is excreted in the urine and exerts a toxic effect on renal epithelial cells with direct tubular damage. Depending on urine and plasma concentration of oxalate, kidney involvement may consist of recurrent oxalate urolithiasis or tubulointerstitial oxalate deposits. Both conditions carry the risk of kidney failure. Acute oxalate nephropathy (AON) is a devastating entity characterized by massive oxalate deposits and acute kidney injury with dismal prognosis (3–6). AON is the most threatening complication in patients with primary hyperoxaluria (7). It may also result from ethylene glycol intoxication (8). Enteric conditions responsible for AON include chronic inflammatory bowel diseases, short-bowel syndrome, and bariatric surgery with jejunoileal bypass or Roux-en-Y gastric bypass (5,9). In addition, AON has been reported in 10 patients with chronic pancreatitis but only as case reports or in small series (3,4,10–14).

Chronic pancreatitis (CP) is a heterogeneous disorder characterized by intermittent or persistent abdominal pain and progressive tissue damage leading to pancreatic fibrosis with loss of exocrine and endocrine pancreatic function. The terminal stage of chronic pancreatitis is characterized by maldigestion and diabetes mellitus. AON is an uncommon complication of chronic pancreatitis. The pathophysiological mechanisms, risk factors, and the clinical course of AON in chronic pancreatitis are poorly known, precluding adequate management.

In this observational study, we extensively describe the clinical, biologic, and pathologic findings in 12 patients with both chronic pancreatitis and AON. In four cases, AON prompted recognition of chronic pancreatitis and exocrine pancreatic insufficiency, highlighting the need of accurate assessment of pan-

creatic exocrine function in all patients with acute interstitial nephritis and birefringent crystalline deposits suggestive of calcium oxalate deposits.

Materials and Methods

We retrospectively reviewed the clinical charts of all patients with a diagnosis of AON and chronic pancreatitis who came to attention between January 2004 and August 2010 in three renal units settled in southwest France (University Hospitals in Toulouse and Pont-de-Chaume Clinic in Montauban) and one in Paris (Georges Pompidou-European University hospital). This study was approved by our internal review board and fulfilled the criteria of the Declaration of Helsinki.

Clinical history was recorded through a standardized screening of the patient's hospital records. Age of the patients refers to the age at the admission for AON. If present, a past history of urinary stones was recorded. Hypertension was defined by a BP higher than 140/80 mmHg and/or the use of antihypertensive medications. Hematuria and leukocyturia were assessed by urinary dipstick analysis. Proteinuria was assessed by measurement of a 24-hour urine sample. Estimated GFR (eGFR) was calculated by the simplified Modification of Diet in Renal Disease (MDRD) formula. Renal failure was defined by eGFR <60 ml/min per 1.73 m^2 and stages of chronic kidney disease were defined according to Kidney Disease Outcomes Quality Initiative (KDOQI) classification (15). In patients requiring hemodialysis, eGFR was arbitrarily set at 0. Hypocalcemia and hyperoxaluria were defined by serum calcium level <2.1 mmol/L and urinary oxalate excretion >500 μmol/d (or >45 mg/d), respectively. Kidney and pancreas imaging studies (ultrasonography or computed tomography) were reviewed. Diabetes mellitus was diagnosed on the basis of receiving either insulin or oral antidiabetic agents, or biochemical evidence of diabetes in accordance with World Health Organization guidelines. All medications were recorded.

Renal pathology consisted of light microscopy and immunostaining directed against IgG, IgA, IgM, kappa and lambda light chains, and fibrinogen. In the patient with kidney graft, C4d immunostaining was also performed. Polarization was routinely done when unexpected crystals were detected.

Diagnosis criteria for AON were as follows: (*1*) rapidly progressive renal failure (defined by a >75% increase of serum creatinine in <6 months); (*2*) tubulointerstitial nephritis with massive birefringent crystalline deposits within tubular lumen, tubular epithelial cells, and/or interstitial space on kidney biopsy; and (*3*) exclusion of other causes of acute kidney injury, *i.e.*, obstructive nephropathy, acute rejection in patients with kidney graft, and toxic or drug-induced tubulopathy.

Criteria to diagnose chronic pancreatitis required at least one clinical feature (episodic or persistent pain, attacks of acute pancreatitits, diabetes mellitus, steatorrhea) and demonstration of pancreatic function loss by a direct pancreatic function test (daily fecal elastase excretion <200 μg/g of stools or massive steatorrhea >6 g/d) or well defined pancreas imaging abnormalities (*i.e.*, ductal dilation or irregularity; or parenchymal changes including atrophy, cysts, or calcifications of the gland upon computed tomography scan) (16).

All data are shown as medians and ranges.

Results

From January 2004 to August 2010, we identified 12 individuals (three women and nine men, median age 67 years [41 to 90]) with AON and concomitant chronic pancreatitis. Before the onset of AON, median serum creatinine was 96 μmol/L (70 to 179). Median eGFR was 57 ml/min per 1.73 m^2 (36 to 89). Seven of 12 patients had stage 3 chronic kidney disease (CKD). Eight patients were on treatment for hypertension. One patient had received kidney and pancreas grafts for type 1 diabetic nephropathy 8 and 3 years before AON, respectively. The pancreas graft was removed shortly after engraftment because of arterial thrombosis.

Clinical and biologic data at diagnosis and at the end of follow-up are presented in Tables 1, 2, and 3.

Renal Presentation

At diagnosis of AON, renal function was severely impaired (median serum creatinine 587 μmol/L [294 to 849]). Three patients were oliguric. Seven had low-range proteinuria (<1 g/d), one had high-range proteinuria (>1 g/d), three had microscopic hematuria, and seven had leukocyturia without concomitant urinary tract infection. Urinalysis failed to identify cellular casts or crystalluria. Nine patients had hypocalcemia (75%). Among them, frank hypocalcemia (<1.5 mmol/L) was found in four patients. No patient had worsening of pre-existing hypertension.

Renal imaging showed bilateral kidney atrophy in three patients and normal-sized kidneys in nine. Nonobstructive nephrolithiasis was detected in three cases.

A kidney biopsy was performed in all of the patients. By light microscopy, the most prominent findings consisted of acute tubular injury (including tubular necrosis, cortical tubule dilation, diminishment or loss of the proximal tubule brush border, and flattened regenerating epithelium), interstitial inflammatory cell infiltrate, and interstitial edema. In all kidney specimens, light microscopic examination also showed large clear crystals within the tubule lumen (see Figure 1), interstitium, and tubular epithelium cells with adjacent tubular basal membrane damage. Birefringency of the crystalline deposits under polarized light (see Supplemental Figure 2) was suggestive of calcium oxalate deposits. In addition, glomerulosclerosis was identified in six patients and features of diabetic nephropathy in three. In the patient who had received a kidney transplant, renal C4d immunostaining was negative and no feature of acute rejection could be found.

Pancreas Involvement

At referral, eight patients had a past history of chronic pancreatitis, including seven with established pancreatic exocrine insufficiency lasting from 2 to 17 years. Six of them received pancreatic enzyme replacement therapy whereas in one patient pancreatic enzyme replacement therapy was withdrawn 2 months before the onset of AON. In four patients, the diagnosis of chronic pancreatitis was established after recognition of AON. Fecal elastase was below the normal threshold in five tested patients. Nine patients had a history of diabetes mellitus (median duration 10 years [6 to 16]) and received oral antidiabetic agents or insulin ($n = 2$ and $n = 8$, respectively). Pancreas

Table 1. Clinical charts of 12 patients with chronic pancreatitis and acute oxalate nephropathy

Patients (n = 12)	
age at onset (year)	67 (41 to 90)
gender (men/women)	9/3
Kidney involvement	
renal status before AON	
serum creatinine (μmol/L)	96 (70 to 179)
eGFR (ml/min per 1.73 m^2, MDRD)	57 (36 to 89)
CKD stage	2 (n = 5)/ 3 (n = 7)
renal status at presentation	
serum creatinine (μmol/L)	587 (294 to 849)
serum calcium (mmol/L)	1.69 (1.09 to 2.62)
serum PTH (pg/ml)	262 (63 to 750)
urine protein (g/d)	0.34 (0.05 to 1.01)
leucocyturia (n)	10
hematuria (n)	3
urine oxalate (mg/day; $n \leq 45$)	80 (52 to 92)
oligoanuria	3
Pancreas involvement	
prior diagnosis of chronic pancreatitis	8
duration (years)	10 (2 to 17)
diabetes mellitus	9
duration (years)	(6 to 16)
treatment (OAD/insulin)	3/6
exocrine pancreatic insufficiency	7
known before AON	
pancreatic enzyme supplementation	6
unknown before AON	5
low fecal elastase at recognition of AON	5
pancreas imaging	
gland atrophy or heterogeneity	9
calcifications	10
Wirsung bud dilatation	2
pseudocysts	1
Potential triggers of AON	
acute diarrhea	5
massive ascorbic acid intake	1
diuretics/RAS blockers	5/8
recent antibiotherapy	4
Renal outcome at last follow-up	
duration (months)	7 (2 to 60)
serum creatinine (μmol/L) in patients free of RRT	212 (98 to 410)
eGFR (ml/min per 1.73 m^2)	17 (0 to 55)
CKD stage 2/3/4 (n)	1/4/4
RRT	3

Median values are presented with their ranges in parentheses. All other values indicate the number of patients, unless specified otherwise. AON, acute oxalate nephritis; CKD, chronic kidney disease; eGFR, estimated GFR; OAD, oral antidiabetic drug; PTH, parathormone level; RAS, renin-angiotensin system; RRT, renal replacement therapy.

imaging (see Figure 1) showed pancreatic calcification (n = 10), pancreas atrophy (n = 4), Wirsung duct dilation (n = 2), or cysts (n = 1). Chronic pancreatitis was from alcoholic origin in two patients and idiopathic in the others.

Oxaluria and Oxalate Metabolism

At recognition of AON, daily urinary excretion of oxalate was >45 mg/d (52 to 92) in the 11 tested patients. None of the patients had a history of ethylene glycol poisoning or chronic digestive disease. However, in addition to pancreatic exocrine failure, one or more endogenous or exogenous factors that can acutely modify oxalate urinary concentration through volume depletion were identified in all of the patients, including diarrhea-induced hypovolemia (n = 5), diuretics use (n = 5), and antihypertensive therapy that reduces glomerular filtration fraction in CKD patients (*i.e.,* angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors, n = 8). Four patients were recently given antibiotherapy active on *Oxalobacter formigenes*, which may represent a risk factor of hyperoxaluria (15). One patient received a high dose of ascorbic acid intravenously (4 g/d for 4 days), an oxalate precursor.

Treatment

Blood volume was restored in all patients with crystalloid infusion according to clinical requirement. Following AON recognition, all individuals received a low-fat and oxalate-free diet. Oral calcium supplementation was started in eight patients. Drugs with potential renal hemodynamic or oxalate metabolism-modifying effects were stopped. Pancreatic enzyme supplementation was pursued in six and started in six patients (with a median delay from referral of 22 days [7–35]). Early renal replacement therapy (RRT) (*i.e.,* before day 10) was required in five patients. Four patients received intermittent hemodialysis because of metabolic acidosis or hyperkaliemia, whereas one patient received early continuous veno-venous hemodiafiltration (CVVHDF) in an attempt to remove disposable oxalate.

Renal Outcome

The median follow-up was 7 months (2 to 60). None of the patients died. Among the four patients who required hemodialysis at referral, three still received chronic hemodialysis at the end of the follow-up. After a 5-month follow-up, the patient treated with early CVVHDF had stage 3 chronic kidney disease (eGFR 55 ml/min per 1.73 m^2). In the nine patients who did not require RRT at the end of the follow-up, last mean serum creatinine and eGFR available were 212 μmol/L (98 to 410) and 25 ml/min per 1.73 m^2 (12 to 55), respectively. In one of these nine patients follow-up urinary data were available and showed a normalization of the urinary oxalate concentration.

Discussion

In this study, we aimed to better characterize the clinical course of AON in patients with chronic pancreatitis.

Acute oxalate nephropathy (AON) is acute tubulointerstitital nephritis characterized by abundant calcium oxalate deposits (5). By light microscopy, calcium oxalate crystals are gray-white and spiculated. Most importantly, they are

Table 2. Clinical charts of 12 patients with chronic pancreatitis and acute oxalate nephropathy

Patients	1	2	3	4	5	6	7	8	9	10	11	12
Gender	Male	Male	Male	Female	Female	Male	Male	Male	Male	Male	Male	Female
Age (years)	56	76	67	62	50	90	56	73	83	69	41	80
Pancreas involvement												
prior diagnosis of chronic pancreatitis	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
duration (years)		17	4	10	2			Unknown	Unknown	Unknown	>13	
diabetes mellitus	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
duration (years)	Unknown	Unknown	6	Unknown	Unknown		16			Unknown	9	16
treatment (OAD/insulin)	Insulin	Insulin	OAD	OAD	Insulin	Insulin				Insulin	Insulin	Insulin
exocrine pancreatic insufficiency known before AON	No	Yes	Yes	No[a]	No	No	No	Yes	Yes	Yes	Yes	No
pancreatic enzyme supplementation unknown before AON	Yes	NA	NA	Yes	NA	Yes	Yes	NA	NA	NA	NA	Yes
low fecal elastase at recognition of AON												
pancreas imaging												
gland atrophy or heterogeneity	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes
calcifications	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wirsung duct dilatation	No	No	No	Yes	No	No	No	No	Yes	No	No	No
pseudocysts	No	No	No	No	No	No	No	No	No	No	Yes	No
Potential triggers for AON												
acute diarrhea	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	No	No
oxalate precursor excessive intake	No	No	No	No	Yes	No	No	No	No	Yes	No	No
diuretics/RAS inhibitors	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes
recent antibiotherapy	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No

AON, acute oxalate nephropathy; RAS, renin-angiotensin system; OAD, oral antidiabetic drugs; NA, not available.
[a]This patient had stopped his pancreatic enzyme supplementation 2 months before recognition of the AON.

Table 3. Renal features, treatment, and outcome in 12 patients with chronic pancreatitis–related acute oxalate nephropathy

Patients	1	2	3	4	5
Renal status before AON					
interval between the last SCr assessment and AON	6 months	10 months	6 months	4 months	1 month
SCr (μmol/L)	179	115	80	110	70
eGFR (ml/min per 1.73 m^2)	36	57	89	46	82
CKD stage	3	3	2	3	2
Renal status at presentation					
serum creatinine (μmol/L)	317	796	407	690	294
calcemia (mmol/L)/PTH (pg/ml)	1.58/406	1.09/NA	1.9/750	2.32/389	2.62/143
urine protein/leukocyturia/ hematuria	NA/no/no	0.34/yes/no	0.25/yes/no	0.46/yes/no	0.19/yes/yes
oxaluria ($n < 45$ mg/d)	52	90	89	NA	75
oligoanuria	No	No	No	No	Yes
Renal imaging	(US) Normal	(US/CT scan) Loss of differentiation	(CT scan) Normal	(US/CT scan) Normal	(US) Normal
Renal biopsy	ATN, CaOx crystals, no rejection, diabetic glomerulopathy	TIN, CaOx crystals	TIN, CaOx crystals	TIN, CaOx crystals, glomerulosclerosis	TIN, CaOx crystals
Renal replacement therapy	No	Conventional HD	No	No	CVVHDF
Renal outcome at last follow-up					
duration of follow-up	10	7	15	55	5
CKD stage	5 Chronic HD (from month 6)	5 Chronic HD (from day 6)	3	5 Chronic HD (from month 3)	2
SCr (μmol/L)			212		98
eGFR (ml/min per 1.73 m^2)	0	0	21	0	55

birefringent under polarized light, whereas calcium phosphate crystals do not polarize (5,17,18). In this series, all patients had biopsy-proven AON. Most presented with a typical tubulointerstitial profile consisting of severe renal failure with persistent diuresis, no renal dilation by ultrasonography, low-grade proteinuria, and no or low-grade hematuria. Although eight of 12 patients had a definite history of type 2 diabetes mellitus (and one of type 1), it should be clearly stated that renal presentation of AON highly differs from diabetic glomerulopathy (high-range proteinuria with slowly progressive renal failure). On the basis of our experience, two unusual findings in acute kidney failure may suggest AON before kidney biopsy: (*1*) severe hypocalcemia (<1.5 mmol/L) as observed in one third of our patients and (*2*) urinary oxalate excretion above 45 mg/d. Because renal biopsy may be delayed in diabetic patients because of concomitant antiaggregant therapy ($n = 3$ in this study), oxaluria should be tested early during the course of acute renal failure with tubulointerstitial profile of unclear origin.

Scarce or isolated tubular deposits of oxalate crystals is not a rare finding in the normal or failing kidney at any stage, and even in the transplanted kidney. Isolated oxalate crystals do not imply renal damage, although oxalate deposits in kidney grafts have a negative effect on long-term renal function (18,19). In contrast, abundant tubular or interstitial deposits of calcium oxalate are highly suggestive of a hyperoxaluric condition in native or transplanted kidney.

Plasma oxalate in humans has two sources. The main site of oxalate synthesis is the liver peroxysome, where oxalate is an end product of a number of amino acids, sugars, and ascorbic acid. Oxalate is also present in the gut, mostly complexed to calcium and therefore not absorbed. Malabsorption of fat facilitates fatty acids to bind calcium, leaving oxalate uncomplexed and free to be absorbed. Oxalate plasma concentration is <5.5 μmol/L in adult individuals. In the rodent kidney, plasma oxalate is freely filtered within the glomerulus and then reabsorbed or secreted within various segments of proximal tubules in part because of SLC26A transporters (20). In patients with advanced renal failure, urinary excretion of oxalate decreases, leading to plasma and interstitial oxalate accumulation. Given its poor solubility, a serum oxalate concentration above 30 μmol/L carries the risk of crystallization ensuing in systemic oxalosis. Oxalate precursors incriminated in toxic or drug-induced AON include acute poisoning by ethylene glycol (8) and ascorbic acid (21), respectively. Enteric hyperoxaluria has been described in various malabsorptive intestinal diseases, like jejuno-ileal bypass (17,22), short bowel syndrome (23,24), and chronic inflammatory bowel disease (25–27). Recently, short series have emphasized the risk of AON after modern bariatric surgery with Roux-en-Y gastric bypass (5,9).

Chronic pancreatitis with exocrine pancreatic insufficiency may also be associated with hyperoxaluria and AON. In this series, eight of 12 patients had evidence of chronic pancreas disease at AON recognition, including six with pancreatic enzyme replacement therapy. Exocrine pancreas insufficiency was further proven in the four remaining patients for whom fecal elastase was extremely low. These findings, along with median age in this series

Table 3. (Continued)

6	7	8	9	10	11	12
6 months	6 months	2 years	6 months	1 year	7 months	8 months
112	88	96	119	95	133	90
57	82	71	42	72	55	56
3	2	2	3	2	3	3
734	655	750	421	849	587	345
1.46/283	2.44/125	1.16/NA	2.02/160	1.95/NA	1.65/262	1.69/63
1.01/yes/yes	0.66/yes/yes	0.35/yes/no	0.17/yes/no	0.05/yes/no	0.34/yes/no	0.27/no/no
88	24	85	ND	62	80	45
No	No	Yes	No	Yes	No	No
(US)	(US/CT scan)	(CT scan)	(US/CT scan)	(US)	(CT scan)	(CT scan)
Renal atrophy and loss of differentiation	Bilateral lithiasis Hyperechogenicity	Unilateral lithiasis	Loss of differentiation	Normal	Unilateral lithiasis	Normal
TIN, CaOx crystals, glomerulosclerosis	TIN, CaOx crystals	ATN, CaOx crystals, glomerulosclerosis	ATN, CaOx crystals, glomerulosclerosis	TIN, CaOx crystals, glomerulosclerosis, diabetic glomerulopathy	TIN, CaOx crystals	TIN, CaOx crystals glomerulosclerosis, diabetic glomerulopathy
No	Transient conventional HD	Transient conventional HD	Transient conventional HD	No	No	No
4	2	16	36	60	6	2
4	3	4	5	5	4	4
200	188	325	367	410	227	180
29	34	17	13	12	28	25

Urine protein value is given in g/d. ATN, acute tubular necrosis; CaOx, calcium oxalate; CKD, chronic kidney disease; CT, computed tomography; CVVHDF, continuous venovenous hemodiafiltration; eGFR, estimated GFR; HD, hemodialysis; NA, not available; PTH, parathormone level; RAS, renin-angiotensin system; SCr, serum creatinine; TIN, tubulointerstitial nephritis; US, ultrasonography.

and pancreatic calcifications in 10 of 12 patients, strongly argue for AON being a late complication of chronic pancreatitis.

In chronic pancreatitis, the pathogenesis of hyperoxaluria remains uncertain. It is admitted that fat malabsorption leads to an increase in intraluminal free fatty acid content that competitively inhibits the precipitation of dietary calcium with oxalate. Consistent with this hypothesis, urinary oxalate levels are significantly increased in patients receiving a gastrointestinal lipase inhibitor (28). As a result, a high amount of soluble uncomplexed oxalate remains available in the intestinal lumen. Because bile salts and free fatty acids induce colonic mucosa hyperpermeability, dietary oxalate absorption increases from 10% to 40%, leading to hyperoxalemia, hyperoxaluria, and subsequent urinary oxalate crystallization (29–32).

Except in the patient who had a massive ascorbic acid intake, the event triggering AON in patients with chronic pancreatitis is not yet clear. All changes that modify oxalate metabolism and abruptly increase the plasma oxalate concentration may lead to sudden kidney interstitial and urinary oxalate supersaturation. First, because one patient developed AON within 8 weeks after stopping enzyme supplementation, whether insufficient enzyme therapy was a trigger of AON in the remaining patients is open to question. Second, the role of intestinal colonization by *Oxalobacter formigenes* (OF) in oxalate gut absorption has been emphasized (33). OF degrades intraluminal soluble oxalate and decreases the colonic oxalate absorption (34). Oral or intravenous antibiotherapy is the main cause of OF absence (35) and could trigger AON in four of the patients. This finding remains speculative as a marked increase in urine oxalate after antibiotic use has not been shown. Third, recent dehydration (vomiting, diarrhea, and diuretics) or renin-angiotensin system (RAS) inhibitors intake are frequently reported in patients with AON (5,10,13). Increased intratubular concentration of oxalate, secondary to enhanced reabsorption of sodium and water in the proximal tubule, likely explains the propensity of AON to be triggered by extracellular depletion. In this series, all patients received at least one RAS inhibitor or diuretics.

Treatment of AON remains largely empirical. Because the ultimate goal is to decrease both plasma and urine oxalate concentration, the following management should be promptly achieved: (*1*) restore optimal GFR by stopping antihypertensive medication interfering with renal hemodynamics and ensuring high diuresis output with crystalloids infusion; and (2) decrease oxalate intestinal absorption by using a low-fat, low-oxalate diet, providing high oral calcium intake (>1.5 g/d), and starting adequate pancreatic enzymatic supplementation (36). Whether long-term use of high-dose calcium or probiotics containing OF is beneficial or detrimental remains unknown. In patients with hyperoxaluria, the use of OF probiotics failed to reduce daily urinary oxalate excretion (37).

In the very early phase of management of AON, it is tempting to hypothesize that intensive plasma oxalate removal by hemodialysis may promptly reduce the plasma

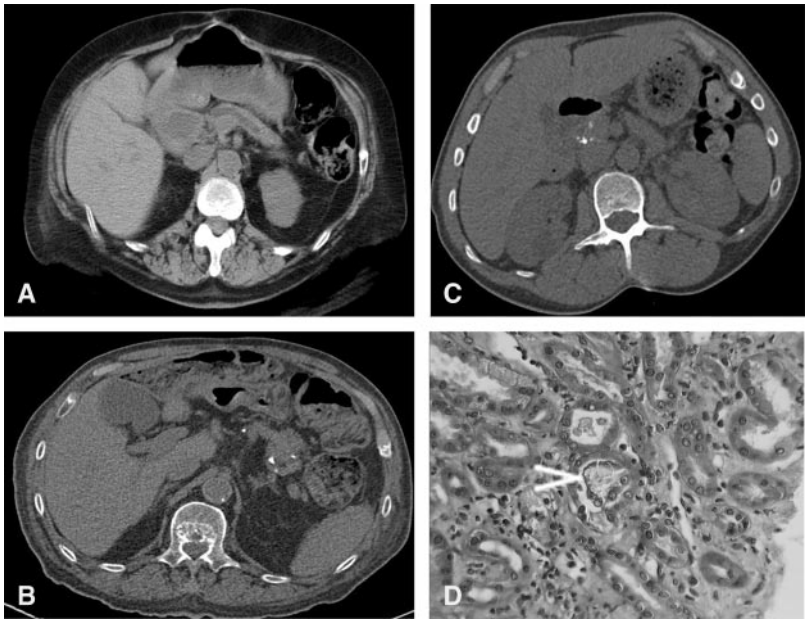

Figure 1. | **Pancreas imaging (A, B and C) and renal pathology (Massons's trichrome staining) (D) in patients with acute oxalate nephropathy related to chronic pancreatitis.** (A) Dilation of the Wirsung duct; (B) corporeal and (C) head calcifications of the pancreas; (D) calcium oxalate crystal (→) within a tubular lumen with flattened epithelium, interstitial edema, and inflammatory cells.

oxalate level and hyperoxaluria until a more specific treatment is efficient. In line with this hypothesis, one patient received early CVVHDF. A similar approach has been recommended in patients with primary hyperoxaluria type 1, to eliminate the dramatic increase of serum oxalate concentration resulting from tissue deposits removal occurring after kidney transplantation (38,39). Given the small size of our cohort, we could not assess the efficiency of early CVVHDF. Whether early and intensive RRT may be useful in chronic pancreatitis–related AON and severe renal failure warrants better assessment.

Overall, prognosis of AON is poor. AON mostly occurs in patients with pre-existing CKD, mainly related to diabetic nephropathy (5,13). Consistent with data issued from patients with jejuno-ileal bypass (5), pre-existing CKD seems to be a prognosis factor of renal function worsening: in our series three of seven individuals with stage 3 CKD subsequently required RRT at the end of the follow-up and three reached stage 4 CKD. Among the 10 cases of chronic pancreatitis–related AON previously reported (3,4,10–14), six patients progressed to end-stage kidney disease at the end of the follow-up. Thus, the cumulative rate of patients with CP-related AON reaching end-stage renal disease in published series and in our cohort reaches 41% (9 of 22), a feature close to the outcome of gastric bypass–related AON (5). Overall, gastric bypass and CP-related AON share common features (*i.e.*, risk factors, treatment, and prognosis) but the latter may benefit from an early intake of pancreatic enzyme allowing partial AON reversal.

Renal transplantation has been proposed in few patients with end stage-renal failure and enteric hyperoxaluria, but recurrent oxalate deposition leading to graft loss may occur (3,24,25,40). Serum oxalate should thus be reduced before transplantation by means of an oxalate-free diet, calcium supplementation, and maybe high-flux daily dialysis. After transplantation, pancreatic supplementation should be continued.

Renal units involved in this study have neither specific referral bias nor practice pattern that may account for aggregation of AON in their population. However, two main limits have to be considered. First, this is not an epidemiologic study and the prevalence of both hyperoxaluria and AON in patients with chronic pancreatitis cannot be addressed. Second, we retrospectively reviewed the cases of AON followed in nephrology units for acute renal failure. Accordingly, this series was biased and focused toward the most severe phenotype of AON. Mild to moderate AON may not come to the attention of nephrologists. Moreover, AON superimposed on diabetic glomerulonephritis could be missed. A prospective assessment of oxaluria in patients with newly diagnosed chronic pancreatitis may address this question.

In summary, we report 12 cases of acute oxalate nephropathy related to chronic pancreatitis and provide keys for early recognition (rapid progressive renal failure, tubulointerstitial profile, severe hypocalcemia, hyperoxaluria, and oxalate deposits on renal biopsy) and optimal management. Risk factors amenable to prevent this severe renal disease are well identified. We show here that AON was the presenting manifestation of chronic pancreatitis in four of 12 patients, highlighting the need of pancreas function assessment in patients with acute tubulointerstitial nephritis and oxalate deposits. Conversely, AON occurred in six patients with pancreatic enzyme supplementation, suggesting that a close monitoring of renal function and oxaluria should be performed in patients with chronic pancreatitis.

Disclosures

None.

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